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Assessing the potential of upper respiratory tract point-of-care testing: a systematic review of the prognostic significance of upper respiratory tract microbes

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Abstract

Background

Microbial point-of-care testing (POCT) has potential to revolutionise clinical care. Understanding prognostic value of microbes identified from the upper respiratory tract (a convenient sampling site) is a necessary first step to understand potential for upper respiratory tract POCTs in assisting antimicrobial treatment decisions for respiratory infections (RTIs).

Objectives

To investigate the relationship between upper respiratory tract microbial detection and disease prognosis, including effects of antimicrobial use.

Data sources

MEDLINE and Embase databases.

Study eligibility criteria

Quantitative studies reporting microbiological and prognostic data from patients of all age groups presenting with RTI.

Participants

Patients presenting to healthcare or research settings with RTI.

Interventions

Upper respiratory tract swab.

Methods

Systematic review and meta-analysis.

Results

Searches identified 5156 articles, of which 754 were duplicates and 4258 excluded on title or abstract. 144 full texts were screened;21 articles retained. Studies reported data for 15 microbes and 26 prognostic measures (390 potential associations). 107 (27%) associations were investigated statistically, of which 38 (36%) were significant. Most studies reported only prognostic value of test positive results. Meta-analyses suggested hospitalisation duration was longer for patients with respiratory syncytial virus than adenovirus and influenza, but significant heterogeneity was observed between studies.

Conclusions

A quarter of potential prognostic associations have been investigated. Of these, a third were significant, suggesting considerable potential for POCT. Future research should investigate prognostic value of positive and negative tests, and interactions between test result, use of antimicrobials and microbial resistance.

Words 237/300

Introduction

Point-of-care tests used by primary care clinicians to target antimicrobial prescribing could revolutionise the treatment of respiratory tract infections (RTI), improving patient outcomes and reducing drug side-effects and antimicrobial resistance. Primary care clinicians are responsible for the majority of human antibiotic use in the UK, US and Europe. Paediatric RTI is the most common presentation managed by primary care physicians.[1 2] Antibiotics are prescribed at up to 67% of RTI consultations,[3] yet there is strong evidence that a large proportion of these prescriptions are unnecessary.[4 5] Antibiotic overprescribing has been partially attributed to uncertainty described by clinicians in identifying patients who may subsequently develop serious illness, and require hospital intervention.[6] Policy makers, primary care clinicians and the research community are calling for evidence to help differentiate patients who would benefit from antimicrobials from those who would not.[5 7 8]

There is currently no way for a primary care clinician to distinguish viral from bacterial aetiology for respiratory infections in a timely manner. The burden placed on primary care means that evidence-based algorithms and tests are actively being sought; for example, an algorithm to identify children at risk of hospitalisation has recently been developed in a large observational study.[9] However this algorithm does not differentiate bacterial from viral infection. Additionally, C-reactive protein blood testing to target prescribing in adults and children is being investigated [10] but is not routinely used in the UK. A third possible strategy, and the subject of this review, is to rapidly test respiratory microbiological samples. Point-of-care test technology is rapidly developing: test devices are now able to detect common respiratory tract microbes in 20 minutes to two hours, [11] and could therefore be of value in primary care.

Upper respiratory tract samples are acceptable to patients and are easily obtained in primary care.[9] Recent evidence suggests that specific microbes are weakly associated with clinical characteristics of children with RTI at presentation to primary care, and may be aetiological.[12] However, the association between the detection of these microbes and: (i) patient prognosis; and (ii) patient response to antimicrobial treatment is unknown. If detection of specific microbes from the upper respiratory tract was associated with response to antimicrobial treatment, tests for these microbes could be used to target antimicrobial prescribing.

Research question

To determine whether specific microbes detected from the upper respiratory tract are associated with the prognosis in patients of all ages presenting to all healthcare services with RTIs. Secondary questions are whether prognosis is affected by prescription of antimicrobials or the resistance status of the microbes detected.

Methods

Eligibility criteria

Studies eligible for inclusion were peer-reviewed, quantitative studies reporting microbiological and prognostic data from patients of all age groups presenting to a healthcare service or research team in an Organisation for Economic Co-operation and Development member country, with diagnosis or symptoms of RTI. Studies recruiting from primary care, secondary care, and community settings such as hospital outpatient or community research clinics were included. Studies were excluded where participants were recruited solely from intensive care or from a population with a high prevalence of pre-existing chronic disease or immune incompetence. Full inclusion and exclusion criteria are given in Table 1.

Search strategy

Our search strategy was designed to identify studies and systematic reviews that reported the relationships between microbes sampled from the upper respiratory tract in patients with respiratory tract infection, and prognostic outcomes. MEDLINE and Embase databases were searched using the OVID platform to 15 March 2018.

The MEDLINE search strategy is presented in Appendix 1 and used combinations of MeSH (Medical Subject Headings) terms and text words for clinical diagnoses of respiratory infection; 20 different microbes implicated in respiratory tract infection (identified by consultant microbiologists and used in previously published work);[13] and MeSH terms and text words for prognosis. The search excluded papers focusing on cystic fibrosis and tuberculosis. This search strategy was developed, extensively tested and refined using an iterative process with input from the University of Bristol subject librarian and search expert, and was subsequently adapted for use in Embase. The search was limited to humans, and no time restrictions were applied. Reference lists of all included full-text articles were also screened.

Study selection

Titles and abstracts of all identified studies were assessed for eligibility by one author (HT) and those which did not fulfil the inclusion/ exclusion criteria were excluded. Full-text copies of included articles were independently reviewed. Dual screening was performed for 20% of all records by three authors (IL, AB and CH) and eligibility disagreements resolved by discussion.

Data extraction and quality assessment

Data were extracted from full texts using a purpose-designed Access form. Descriptive variables were: country of recruitment; study setting (e.g. primary/ secondary care), study design, anatomical respiratory tract sampling location, laboratory methods, microbes identified, diagnoses of participants, number of participants, participant age inclusion criteria, type of prognostic outcomes reported, and whether results were stratified by antibiotic prescribing or consumption. Outcome data extracted were any measure of prognosis, including but not limited to symptom duration, hospitalisation and length of hospital stay. The number of outcomes reported by studies for each microbe, and any association found between microbe and outcome, was recorded and reported in a 'vote count' table. Where the same outcome was reported for the same microbe by three or more studies, with means and standard deviations, random-effects meta-analysis was carried out using STATA (Stata Statistical Software: Release 13. College Station, TX: StataCorp LP) using the 'metan' command. Quality assessment was conducted for all studies included in the review using the QUIPS tool.[14]

Results

Ascertainment

Our search identified 5156 articles of which 754 were duplicates (**Error! Reference source not found.**). Of the 4402 remaining, 3829 were excluded on the basis of title and a further 429 on the basis of abstract. Full texts of 144 articles were screened and 21 were eligible for inclusion in the review.

Study characteristics and microbiological data

Characteristics of the 21 studies included in this review are summarised in Table 2. The most common recruitment setting was hospital inpatients (13 studies; 62%), followed by hospital outpatient/ community research clinics or primary care centres (five studies; 24%) and emergency departments (two studies; 10%). One study recruited in both primary care centres and an emergency department. The majority of studies (16; 76%) recruited only children, with eight recruiting children aged less than two years.

Most studies used a prospective observational design (17, 81%). Several upper respiratory sampling methods were used: nasopharygeal wash/ aspirate (13 studies, 62%); nasopharyngeal swabs (4 studies, 19%); combinations of nasal, throat, nasopharyngeal swabs and aspirates (three studies, 14%); and a rhino-pharyngeal swab (one study, 5%). Laboratory methods also varied between studies, with 11 (52%) using polymerase chain reaction techniques, 3 (14%) using immunofluorescence, and the remainder using mixed/ other methods.

Data were reported for 15 microbes / groups of microbes, including four bacteria, 10 viruses, and a combined Influenza A/B category. A full list of reported microbes is given in Table 4. The most data were reported for RSV (15 associations with prognosis investigated), rhinovirus (6) and influenza (6). The majority (13, 62%) reported data only for participants who were positive for the microbe(s) of interest; there is therefore a paucity of 'control' data from participants without detected microbes. None of the studies quantified microbial load, and no study reported outcomes stratified by antibiotic consumption or antimicrobial resistance.

Quality assessment is summarised in Table 3. No study had high risk of bias in the domain assessing attrition. The domain assessing confounding showed high risk of bias, commonly because studies measured limited numbers of microbes such that results could have been confounded by the presence of an untested microbe. High risk of bias was observed in three other domains for at least one study. Three studies had low risk of bias in all domains; 10 had high risk of bias in at least one domain.

Outcomes

Prognostic outcomes are listed in Table 4, which shows a 'vote count' of associations examined between reported microbes and outcomes, and whether associations were reported by the primary study authors as statistically significant. In total, 26 differently measured outcomes were reported, the majority of which fell into three categories: (i) hospitalisation duration (nine measures); (ii) symptom duration (eight measures); and (iii) healthcare use (six measures).

The most commonly reported outcome was duration of hospitalisation, which was reported by at least one study for all microbes (Table 4). Symptom duration was reported using at least one measure for 10/15 microbes, and healthcare use was reported using at least one outcome for 9/15 microbes.

Relationship between microbes and prognosis

The 26 outcome and 15 microbe categories reported in Table 4 give a total of 390 possible associations. Of these, 99 (25%) were examined by one or more study, with a total of 134

associations reported by all studies. There were an additional five microbes for which we sought data, but identified no relevant studies.

Statistical tests were used to assess relationships between microbe detection and outcomes for 107/134 outcomes. These were reported by the study authors to be statistically significant ($p<0.05$) in 38/107 (36%). Twenty seven associations were reported in which the authors did not use statistical tests, but reported raw data.

Due to the diversity of outcome measures reported, opportunities for meta-analyses were limited. We considered use of methods designed for synthesis of diversely reported outcomes including the albatross plot,[15] but were unable to proceed due to insufficient primary data.

Meta-analysis was possible for duration of hospitalisation. Means and standard deviations were provided by seven studies for RSV and three for adenovirus. Data were also available from three studies, pooling results for influenza A and B. A forest plot for these analyses is given in Figure 2. Significant heterogeneity was observed for all three pooled estimates and as such they should be interpreted with caution.

One additional study (Laundy et al[16]) provided mean duration of hospitalisation for patients with RSV and influenza A, but could not be included in the meta-analysis as no standard deviation was reported. When compared with the results of the meta-analysis, the mean duration of hospitalisation for RSV (2.2 days) and influenza A (6.0 days) do not fall within the confidence intervals for the pooled estimates. However, the Laundy study was small, with eight participants identified with influenza A and nine with RSV, which means the contribution of the study, if incorporated into meta-analysis, would be low.

It was not possible to examine whether antibiotic prescribing or antimicrobial resistance status influenced prognosis as the studies did not report results stratified by these factors.

Discussion

Summary of main findings

Our review highlights a paucity of evidence for the prognostic value of upper respiratory tract microbes: of the potential 390 possible associations only 27% have been investigated. That said, of those that have been tested, 36% were reported as significant.

Our meta-analysis suggests hospitalisation duration is longer for patients with respiratory syncytial virus than adenovirus and influenza, but we found significant heterogeneity between studies. This is likely to result from the differences in study recruitment setting, country, laboratory methods and participant diagnoses described in Table 2.

Findings in relation to existing literature

Previous work has demonstrated that some specific bacteria and viruses are present more often in the throats of children with acute cough and RTI than in asymptomatic children, [12 13 17] providing some evidence that acute cough alters the flora of the upper respiratory tract and microbes detected there may be aetiological. However, we have also demonstrated here that there is an absence of evidence as to whether targeting antimicrobial treatment to the results of upper respiratory tract microbial testing would lead to improved outcomes.

Strengths and weaknesses

This review was rigorously conducted and reported according to Cochrane and PRISMA guidelines. [14 18] The search strategy was designed by subject experts and the quality of included studies assessed using the appropriate QUIPS tool.[14] We used a 'vote count' table as the most succinct way to present the overall results of the review, though this does mean that small studies lend as much visual weight to results as their larger counterparts.[19]

It is possible that by restricting inclusion, we could have reduced the heterogeneity between studies. However, doing so would have limited our results to a focused population or outcome, limited opportunities for meta-analysis even further, and reduced generalisability of any findings to the broader population.

26 different prognostic measures were identified in the literature. At present, no core outcome set exists for RTI, which leads different studies to measure slightly different outcomes. We aimed to capture all relevant published data in this review, yet had studies (and hence this review) focused on an internationally agreed set of outcomes, it is likely that the percentage of potential associations investigated would have been higher. The large number of associations reported is both a finding in itself, and a limitation of this work.

We were unable to assess the impact of antimicrobial use or antimicrobial resistance on prognosis for patients with/ without bacterial detection as studies did not report results stratified by antibiotic use or resistance status.

Clinical and research implications

Our results suggest significant potential for using upper respiratory tract microbes as the target of future POCT studies.

The currently un-investigated microbial-prognosis associations should be urgently subjected to rigorous research, which should include assessments of the impact of microbial load, antibiotic use, resistance status, the value of negative results. Despite a rigorous search, we identified few studies which reported prognostic data for bacterial identification, with the majority of data reporting viral infections. Future studies should also seek and report as large a range of microbes as possible, to

minimise confounding by the presence of an untested microbe, and more studies are needed in the primary care setting.

Conclusions

A quarter of potential prognostic associations have been investigated, and of these a third were significant, suggesting considerable potential for POCT. Future research should investigate the prognostic value of both positive and negative tests in both primary and secondary care, and look for interactions between test result, use of antimicrobials and microbial resistance.

License to publish

Contributorship statement

ADH conceived the idea for the study, secured funding and supervised its conduct and reporting. HVT conducted the study and led the drafting of the manuscript. HVT, SH, AB and CH conducted the literature searches, and study data extraction and quality assessment. KT assisted study conduct. All authors provided critical input to the manuscript, and have seen and approved its final version.

ADH - the corresponding author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; and that no important aspects of the study have been omitted.

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Tables

Table 1: Inclusion and exclusion criteria

Inclusion criteria

1. Peer-reviewed quantitative studies reporting individual-level microbiology from upper respiratory tract samples
2. Participants presenting to a healthcare service or research team with a respiratory tract infection
3. Studies reporting raw data cross-tabulating one or more prognostic outcomes (e.g. illness duration, hospitalisation) against RTI-related upper respiratory tract microbes

Exclusion criteria

1. Microbiology results from lung, blood, urine or faecal samples
2. Microbiology presented as pooled data (as opposed to by individual microbe)
3. Study participants recruited from a population with a high prevalence of pre-existing disease or immune incompetence in whom microbe sampling / detection may differ from wider population
4. Studies of nosocomial infections
5. Full text not available in English
6. Recruitment in a non-OECD member[20] country

Table 2: Characteristics of studies included in the review

Author, year	Country	Recruitment location	Study design	Study size	Eligible age group	Diagnoses of participants	Sample type	Laboratory methods	Microbe(s)	Prognostic outcome(s) reported	Clear swab 'control' group?	Results stratified by antibiotic use?
Bamberger 2012 [21]	Israel	Inpatient	Prospective observational	366	<24mo	Acute bronchiolitis	NPA	PCR	RSV	Duration of hospitalisation: categories <3d, 4-7d, 7+d; mean PICU stay; supplemental oxygen duration <3d: yes/no	No	No
Bennett 2007 [22]	USA	A&E	Prospective observational	101	<24m	Bronchiolitis	Nasal wash	Viral culture, monoclonal antibody, stain	RSV	Duration of illness: median; hospitalisation: yes/ no	Yes	No
Chan 2007 [23]	Hong Kong	Inpatient	Retrospective case review	561	≤3y	Acute respiratory infection	NPA	Assay & immunofluorescence	RSV and flu A&B (combined)	Duration of fever & duration of hospitalisation: mean (SD), PICU admission y/n	No	No
Chiu 2010 [24]	Hong Kong	Inpatient	Prospective observational	1031	<18y	Febrile upper respiratory tract infection	NPA	Immunofluorescence	RSV, PIV, Adv	Duration of hospitalisation: mean (SD)	No	No
Cohen 2015 [25]	France & Turkey	Community clinic & A&E	Prospective observational	774	Any age	Laboratory-confirmed influenza A or B	Rhino-pharyngeal swab	RT-PCR	Flu A & B	Hospitalisation: yes/no; illness duration split by age group: odds ratio	No	No
Foshaug 2015 [26]	Norway	Primary care	Retrospective case–control	414	Adult	'Airway infections'	NPS	PCR	*M. pneumoniae*	Admission to hospital (yes/ no)	Yes	No
Franz 2010 [27]	Germany	Inpatient	Prospective observational	404	0-16y	Lower respiratory tract infections	NPA	RT-PCR	RSV, RV, HBoV, adenoviruses	Duration of hospitalisation: median	No	No
Garcia-Garcia 2017 [28]	Spain	Inpatient	Prospective observational	3906	<14y	Acute respiratory tract infection	NPA	RT-PCR	HMPV, RSV, RV, HBoV, adeno	Duration of fever and duration of hospitalisation: mean (SD)	No	No
Güllü 2017 [29]	Turkey	Inpatient	Prospective observational	361	<2y	Viral lower RTI	NP swab	Rapid antigen detection test	RSV	Duration of hospitalisation: mean and SD	Yes	No
Iwane 2011 [30]	USA	Inpatient	Prospective observational	1867	<5y	Acute respiratory tract infection	NS & TS	RT-PCR	RV	Hospital stay >3d: yes/no; duration of hospitalisation: median (IQR)	No	No

Author, year	Country	Recruitment location	Study design	Study size	Eligible age group	Diagnoses of participants	Sample type	Laboratory methods	Microbe(s)	Prognostic outcome(s) reported	Clear swab 'control' group?	Results stratified by antibiotic use?
Lambert 2007 [31]	Australia	Community clinic	Prospective observational	234	<5y	Acute respiratory infection	Combined NS & TS	PCR	hMPV, coronavirus, picornaviruses (pooled), PIV, ADV, RSV, influenza A	Hospitalisation: yes/no; ED presentation: yes/no; symptom duration: mean and median	Yes	No
Lau 2006 [32]	Hong Kong	Inpatient	Prospective observational	4181	Any age	'Respiratory tract infections'	NPA	RT-PCR	HCoV, Flu A & B, Adv, parainfluenzaviruses, RSV, hMPV	Duration of fever and duration of hospitalisation: mean and SD	No	No
Laundy 2003 [16]	UK	Primary care centre & A&E	Prospective observational	51	<5y	Community-acquired pneumonia	NPA	Indirect immunofluorescence, PCR	RSV, influenza A	Duration of hospitalisation, fever and illness duration: median, mean and range	No	No
Mansbach 2008 [33]	USA	A&E	Prospective observational	277	<2y	Bronchiolitis	NPA	PCR	RSV, RV	Symptom duration: median, IQR; relapse within two weeks: yes/no; days of activity limitation post hospital visit: median (IQR)	No	No
Marguet 2009 [34]	France	Inpatient	Prospective observational	209	1m–1y	First episode acute bronchiolitis	NPA	RT-PCR	RSV, RV, hMPV	Duration of hospitalisation: median (IQR)	Yes	No
Mullins 2011 [35]	USA	University health clinic	Prospective observational	60	Adult	Influenza-like illness	NPS	PCR	Influenza	Days off school/work: mean (CI)	Yes	No
Palomino 2004 [36]	Chile	Inpatient	Prospective observational	117	<2y	Acute lower respiratory infection	NPA	Immunofluorescence	Adv	Duration of hospitalisation: median	No	No
Resch 2011 [37]	Austria	Inpatient	Retrospective notes review	425	<12mo	Lower respiratory infection	NPA	ELISA, immunofluorescence	RSV & influenza	Duration of hospitalisation: mean (SD); supplemental oxygen treatment duration	No	No
Shaikh 2014 [38]	USA	Outpatient	Prospective observational	206	2-12y	Acute sinusitis	NPS	Culture	*S. pneumoniae, M. catarrhalis, H. influenzae*	Days to symptom resolution: median	Yes	No
Tsolia 2003 [39]	Greece	Inpatient	Prospective observational and retrospective case review	636	<1y	Bronchiolitis	NPW	Immunofluorescence	RSV	Duration of hospitalisation: mean (SD); intensive care admission: yes/no	Yes	No

Author, year	Country	Recruitment location	Study design	Study size	Eligible age group	Diagnoses of participants	Sample type	Laboratory methods	Microbe(s)	Prognostic outcome(s) reported	Clear swab 'control' group?	Results stratified by antibiotic use?
Tsung 2010 [40]	Hong Kong	Inpatient	Prospective observational	475	<5y	Acute respiratory tract infections	NPS & NPA	Immunofluorescence, PCR	Adv, influenza A & B, PIV, RSV, hMPV, *M. pneumoniae*, RV, enterovirus	Duration of hospitalisation: categories: <2d, 3-4d, >5d, median (IQR)	No	No

Abbreviations: d: days; w: weeks; mo: months; y: years; NPA: nasopharyngeal aspirate; PCR: polymerase chain reaction; RT-PCR: reverse-transcriptase PCR; hMPV: human metapneumovirus; HBoV: human bocavirus; SD: standard deviation; IQR: interquartile range; RSV: respiratory syncytial virus; RV: rhinovirus; NPS: nasopharyngeal swab; A&E: accident and emergency department; GP: general practice; NP: nasopharyngeal; ELISA: enzyme-linked immunosorbent assay; HCoV: coronaviruses; Adv: adenovirus; PIV: parainfluenzavirus; NS: nasal swab; TS: throat swab; ED: emergency department; NPW: nasopharyngeal wash; PICU: paediatric intensive care unit.

Table 3: Quality assessment of full-text studies using the QUIPS tool.

Author	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Lau 2006	2	1	1	2	3	2
Shaikh 2014	1	1	1	1	3	1
Laundy 2003	1	1	2	2	2	3
Lambert 2007	1	1	1	2	1	2
Mansbach 2008	1	1	1	1	3	2
Bennet 2007	1	1	2	1	2	2
Chan 2007	1	1	2	1	3	2
Garcia-Garcia 2017	1	1	1	1	2	1
Marguet 2009	1	1	1	1	1	1
Tsung 2010	2	1	1	1	2	2
Franz 2010	1	1	1	1	1	1
Lambert 2007	1	1	1	1	1	1
Palomino 2004	1	1	3	1	2	1
Tsolia 2003	2	1	2	2	3	1
Chiu 2010	1	1	2	1	2	1

Resch 2011	1	1	2	2	2	1
Foshaug 2015	1	1	1	1	3	1
Mullins 2011	1	1	2	1	2	1
Iwane 2011	1	1	1	1	3	1
Cohen 2015	2	1	1	1	1	1
Gullu 2017	1	1	2	1	3	1
Bamberger 2012	1	1	1	1	2	1

Risk of bias: high (3), moderate (2) or low (1)

Table 4: Vote count' of associations sought between clinical outcomes and microbes reported by studies

	Outcome measure	RSV	Influenza A	Adenoviruses	Parainfluenzaviruses	Rhinoviruses	Human metapneumoviruses	Influenza B	Coronaviruses	Influenza (pooledA&B/ not specified)	*Mycoplasma pneumoniae*	Bocavirus	Enterovirus	*Streptococcus pneumoniae*	*Moraxella catarrhalis*	*Haemophilus influenzae*
Hospitalisation duration	Hospitalisation duration: Odds ratio		1 1					1 1								
	Hospitalisation duration: >3d (y/n)					1										
	Hospitalisation duration: Categories <3d, 4-7d, 7+d	1														
	Hospitalisation duration: Categories: <2d, 3-4d, >5d	1	1	1	1	1	1	1			1		1			
	Hospitalisation duration: Mean	1	1													
	Hospitalisation duration: Mean (SD)	5 2		2 1	1 1		1 1	1	1	2 1		1				
	Hospitalisation duration: Median	2 1	1	1 1		1						1		1	1	1
	Hospitalisation duration: Median (IQR)	1 1	1	1	1	2 2	1 1	1			1		1			
	Hospitalisation duration: Range	1	1													
Symptom duration	Symptom duration: Mean	1 1	1 1	1	1		1		1							
	Symptom duration: Median	1 1	1 1	1	1		1		1							
	Symptom duration: Median (IQR)	1				1										
	Symptom duration: Range	1	1													
	Duration of fever: Range	1						1								
	Duration of fever: Mean (SD)	2 1	1	2	1	1	2	1	1	1		1				
	Duration of fever: Mean	1	1													
	Duration of fever: Median	1	1													
Healthcare use	A&E presentation: Yes/no	1	1	1	1		1		1							
	Intensive care admission: Yes/no	1 1								1						
	PICU stay duration: Mean	1														
	Supplemental oxygen duration <3d: Yes/no	1														
	Supplemental oxygen duration: Mean (SD)	1								1						
	Hospitalisation: Yes/ no	1 1	1 1 1	1	1		1	1 1	1		1					
Other	Relapse within 2 weeks: Yes/no	1				1										
	Days of activity limitation post hospital visit: Median (IQR)	1				1										
	Days off school/work: Mean (CI)									1						

Key: Numbers report the number of studies seeking an association between a prognostic outcome measure and a microbe detected from the upper respiratory tract. Green number: statistically significant association reported. Red: Non-significant association reported. Black: statistical tests not used. Blank cell: association not sought by any study included in this review.

Appendix 1: MEDLINE search strategy (subsequently adapted for use in EMBASE)

1 Respiratory Tract Infections/ or bronchitis/ or exp bronchiolitis/ or Common Cold/ or Influenza, Human/ or exp Laryngitis/ or exp Pharyngitis/ or exp Pneumonia/ or exp Rhinitis/ or exp Sinusitis/ or whooping cough/
2 (sinusitis or pharyngitis or laryngitis or bronchitis or bronchiolitis or flu or influenza or rhinitis or RTI or pneumonia cough or pertussis or croup or bronchopneumonia).ti,ab.
3 1 or 2
4 letter/
5 editorial/
6 news/
7 exp historical article/
8 Anecdotes as topic/
9 comment/
10 case report/
11 (letter or comment$).ti.
12 animals/ not humans/
13 exp Animals, Laboratory/
14 exp Animal Experimentation/
15 exp Models, Animal/
16 exp rodentia/
17 (rat or rats or mouse or mice or bovine).ti.
18 or/4-17
19 respiratory syncytial viruses/ or respiratory syncytial virus, human/
20 Rhinovirus/
21 Streptococcus pneumoniae/
22 exp Haemophilus influenzae/
23 "Moraxella (Branhamella) catarrhalis"/
24 Mycoplasma pneumoniae/
25 Chlamydophila pneumoniae/
26 exp Staphylococcus aureus/
27 Adenoviridae/
28 exp influenzavirus a/ or exp influenzavirus b/
29 bordetella parapertussis/ or bordetella pertussis/
30 (colonization or colonisation).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
31 ("Haemophilus influenza$" or "hemophilus influenza$" or "h.influenza$" or RSV or "respiratory syncytial virus$" or coronavirus or adenovirus or parainfluenzavirus or parainfluenza virus or metapneumovirus or metapneumonovirus or rhinovirus or bordetella or "s.aureus" or "s. aureus" or staph aureus or Staphylococcus aureus or Streptococcus pneumonia$ or strep pneumonia$ or "s.pneumonia" or "s.pneumoniae" or "s. pneumonia" or "s. pneumoniae" or "m.pneumonia" or "m.pneumoniae" or "m. pneumonia" or "m. pneumoniae" or mycoplasma pneumonia$ or ((group a or beta hemolytic) adj2 streptococc$) or chlamydia pneumonia$ or "c.pneumonia" or "c.pneumoniae" or "c. pneumonia" or "c. pneumoniae").ti,ab.
32 or/19-31
33 prognosis/

34 "Predictive Value of Tests"/
35 duration.ti,ab.
36 or/33-35
37 exp *Genomics/
38 exp *Sequence Analysis, DNA/
39 exp *Tuberculosis/
40 tuberculosis.ti.
41 ("intensive" or "vaccin*").m_titl.
42 ("ventilat*" or "cystic" or "CF").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
43 limit 42 to abstracts
44 or/37-41
45 18 or 43 or 44
46 3 and 32 and 36
47 46 not 45

Nb: the inclusion of a forward slash (/) after a word indicates a Medical Subject Heading (MeSH) search term

Conflict of interest statements

No conflicts of interest declared

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